Case Report Rapport de cas

Pulmonary *Echinococcus multilocularis* metastasis in a dog

Karine Gendron, Christine Goepfert, Elisa Linon, Horst Posthaus, Caroline F. Frey

Abstract — A young adult Labrador retriever dog was presented for surgical debulking of hepatic alveolar echinococcosis. Computed tomography detected hepatomegaly with multiple large cavitary masses with extension of tissue from a lesion wall into the caudal vena cava and numerous nodules in all lung lobes. Following euthanasia, histology confirmed parasitic vesicles with granulomatous reaction in all lesions, and polymerase chain reaction (PCR) established the causative agent to be *Echinococcus multilocularis.* This report is the first to present imaging features of pulmonary *E. multilocularis* granulomata in a dog.

Résumé — Métastases pulmonaires d'*Echinococcus multilocularis* chez un chien. À l'examen par tomodensitométrie d'un Labrador retriever jeune adulte référé pour résection de lésions hépatiques d'échinococcose alvéolaire, une hépatomégalie avec présence de larges masses cavitaires fut mise en évidence, de même que l'extension de la paroi d'une lésion à l'intérieur de la veine cave caudale, et de nombreux nodules pulmonaires. Après euthanasie, des vésicules parasitiques associés à une réaction granulomateuse furent confirmés histologiquement dans toutes les lésions évaluées, et *E. multilocularis* fût démontré par PCR être l'agent causal. Ce rapport de cas est le premier à présenter les caractéristiques de lésions pulmonaires d'*E. multilocularis* chez le chien.

(Traduit par les auteurs)

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A 3.5-year-old neutered Labrador retriever dog was presented to the Small Animal Clinic of the Vetsuisse Faculty, University of Bern, for surgical debulking of hepatic tissue affected by alveolar echinococcosis. The patient had a 3-month history of fatigue and weight loss, and had been dewormed 4 times a year with milbemycin oxime and praziquantel (Milbemax; Novartis Animal Health, Basel, Switzerland) for the first 3 years of its life. Elevated liver enzymes and, on ultrasonography, large hepatic masses were diagnosed by the referring veterinarian; hepatic biopsies revealed *E. multilocularis.* Treatment with albendazole (Valbazen 10%; Pfizer, Zürich, Switzerland), amoxicillin/clavulanic acid (Clavaseptin; Vétoquinol, Lure, France), and robenacoxib (Onsior; Novartis, Basel, Switzerland) was instituted 7 d prior to referral, in an effort to control the infection and the patient's incipient fever.

On presentation, the dog had a body condition score of 1/9 and its abdomen was distended but nonpainful and fluctuant on palpation. Panting persisted at rest, heart rate was 120 beats/min, and temperature was normal. Hematologic profile findings included a non-regenerative anemia [hematocrit 34%, reference interval (RI): 39% to 57%], reticulocytes (8.8×10^9/L) and leucocytosis (21.84×10^9/L, RI: 6.0 to 12.0×10^9/L) with a left shift (6.66×10^9/L, RI: 0 to 0.3×10^9/L), and toxic neutrophilia. Biochemistry revealed hypoalbuminemia (18 g/L, RI: 30 to 40.5 g/L), with normal total proteins (63.8 g/L, RI: 56 to 73 g/L). Alkaline phosphatase (AP) was elevated (614 IU, RI: 13 to 132 IU), but all other hepatic parameters as well as bilirubin were within normal ranges. Computed tomography (CT) was recommended to evaluate resectability of the hepatic masses.

Thoracic and abdominal surveys were performed with a 16-slice CT unit (Philips Brilliance 16; Philips Medical Systems Nederland B.V., Best, Netherlands). The chest was scanned in a caudo-cranial direction under breath hold, with 2 mm slices at 1-mm increments, with 120 kV, 188 mA and a 0.688 pitch. Field of view dimensions were 351 mm with a 512×512 matrix. The scan was repeated approximately 2 min after manual injection of intravenous iohexol [Accupaque 300 mg I/mL, 600 mg/kg body weight (BW), GE Healthcare AG, Glattbrugg, Switzerland]. A total of 73 pulmonary nodules were recorded, most adjacent to the pleura, all at a maximal distance of 9 mm from the pleural surface. Of these 73 nodules, 51 were found in the right lung (including the accessory lung lobe) and 22 in the left lung. Nodules were round, sharply delineated, and subtly lobulated, from pin-point in size to 8 mm in diameter and surrounded by normal lung (Figure 1). Nodules larger than 4–5 mm in most cases presented a hypodense center with occasional mineral dense foci; others were of more homogenous tissular density but in either case, no contrast uptake was

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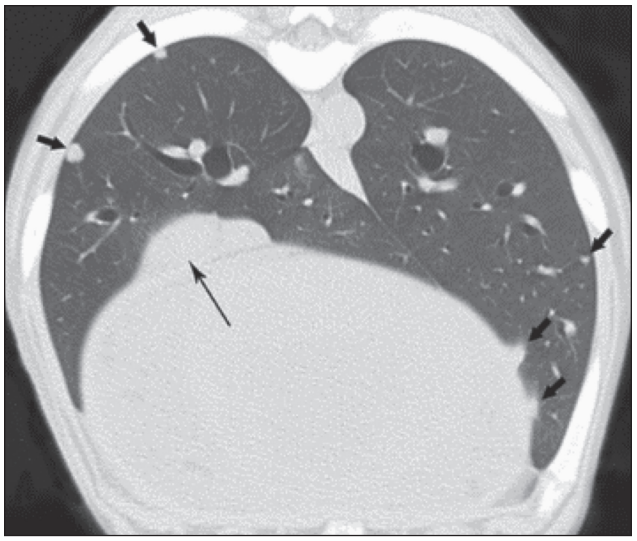

Figure 1. Native CT scan of the caudal lung fields of a 3.5-year-old dog, lung window. The patient's right is to the left on the image. Several small airspace nodules are closely related to the pleural surface (small arrows) representing *E. multilocularis* granulomata. The longer arrow points to the enlarged diaphragmatic lymph node, immediately adjacent to the caudal vena cava.

observed. Sternal lymph node enlargement was observed bilaterally, up to 1.3 cm large with reduced central contrast uptake.

The abdomen was scanned with the following parameters: 3 mm slice thickness, 1.5 mm increment and a pitch of 0.938, with exposure factors of 120 kV and 225 mA. Scans were obtained in native state as well as in arterial and equilibrium (2 min post-injection) phases.

A large amount of peritoneal effusion was present. A cluster of cavitary masses from 7 to 17 cm in diameter occupied the left lateral, caudate, and quadrate lobes of the liver, extending it well beyond the rib cage to the level of the mid-body of L3. A thin, irregular, and moderately enhancing capsule was observed, while the center of the lesions displayed no enhancement (10 HU, consistent with fluid). The portal vein and the caudal vena cava appeared moderately compressed by these lesions, none of which were mineralized. At the level of and cranial to the diaphragm was a 6.5 cm long filling defect in the caudal vena cava lumen, continuous with the capsule of the largest cyst and occupying roughly 1/3 of the cava lumen (Figure 2). An oval soft tissue dense structure was found to the right of the caudal vena cava, flat against the diaphragm and partially indistinguishable from it, with pre- and post-contrast attenuation values similar to that of the diaphragm.

The patient underwent celiotomy 1 wk after CT in an attempted salvage hepatectomy. The gallbladder and greater biliary vessels appeared intact but surrounded by nodular proliferations. The owner was made aware of these findings and elected to have the dog euthanized while still in surgery.

Necropsy revealed a firm yellow, moderately well-demarcated and invasive mass in the caudate lobe of the liver measuring approximately 20 cm in diameter. On cut section, the mass was cystic and filled with clear fluid containing moderate amounts of necrotic debris. The cyst wall consisted of sponge-like, yellow, firm tissue varying from 1 to 5 cm in thickness. The omentum contained multiple yellow nodules of 1 to 3 mm in diameter. Mesenteric and hepatic lymph nodes were markedly enlarged. Multiple yellow, firm nodules of 0.5 to 1 cm in diameter were present in all lung lobes (Figure 3A). In the diaphragm, to the right of the vena cava, was a hard, red-brown nodule 2 cm in diameter.

Histologically, the masses in the liver, the omentum, and lung consisted of main parasitic vesicles and multiple daughter vesicles invading the surrounding parenchyma. Vesicles in the lung (Figure 3B), liver, and omentum were similarly enclosed by a thick layer of fibrous tissue and composed of an outer laminated layer, coated on the inside by a germinal layer and brood capsules arising from the latter. No protoscolices were detected inside the cysts. Parasitic cysts were surrounded by macrophages, multinuclear giant cells, lymphocytes and plasma cells as well as thick layers of fibrous tissue. Several ruptured hepatic cysts were mineralized and necrotic and contained numerous degenerate neutrophils. The diaphragmatic nodule appeared to be a lymph node with severe sinus dilation due to histiocytic and neutrophilic infiltrates.

A multiplex polymerase chain reaction (PCR) able to simultaneously detect *E. multilocularis, E. granulosus,* and *Taenia* spp. DNA (1) was performed on fresh cyst material recovered from the liver. The multiplex PCR targeted mitochondrial genes for NADH dehydrogenase subunit 1 (nad1), and the small subunit of ribosomal RNA (rrnS) (1). For the PCR, genomic DNA was extracted using a DNA purification system (DNeasy® Blood and Tissue Kit; Qiagen, Switzerland) according to the manufacturer's recommended protocol for tissues. Amplification products were visualized on 2% agarose gels stained with ethidium bromide. Expected lengths of amplicons were 395 bp for *E. multilocularis,* 117 bp for *E. granulosus,* and 267 bp for *Taenia* spp. (1). The multiplex PCR showed an amplification product of the same size in the dog reported herein as in the positive control for *E. multilocularis* (Figure 4).

Discussion

Alveolar echinococcosis (AE) is a parasitic disease caused by the larval stage (metacestode) of the small tapeworm *E. multilocularis,* a zoonotic parasite that is endemic in the northern hemisphere (2). Its life cycle involves foxes and other canids as principal definitive hosts, which excrete eggs that are ingested by the intermediate hosts, mainly small mammals and rodents. The domestic dog, a natural definitive host of *E. multilocularis,* may, like humans, also become an aberrant intermediate host, with *E. multilocularis* metacestodes most often proliferating in the liver, causing slowly progressive, life-threatening tumor-like masses (3,4). Echinococcal lesions may occur anywhere in the human body (3), with most common extrahepatic sites being the lungs (7% to 20% of patients) and brain (1% to 3%). Pulmonary AE is often an incidental finding; however, clinical symptoms may include hemoptysis, chest pain, coughing with expectoration, and exertional dyspnea. In CT, human pulmonary AE has been described as single or multiple, unilateral or bilateral pulmonary masses of various sizes, with lobulated or irregular

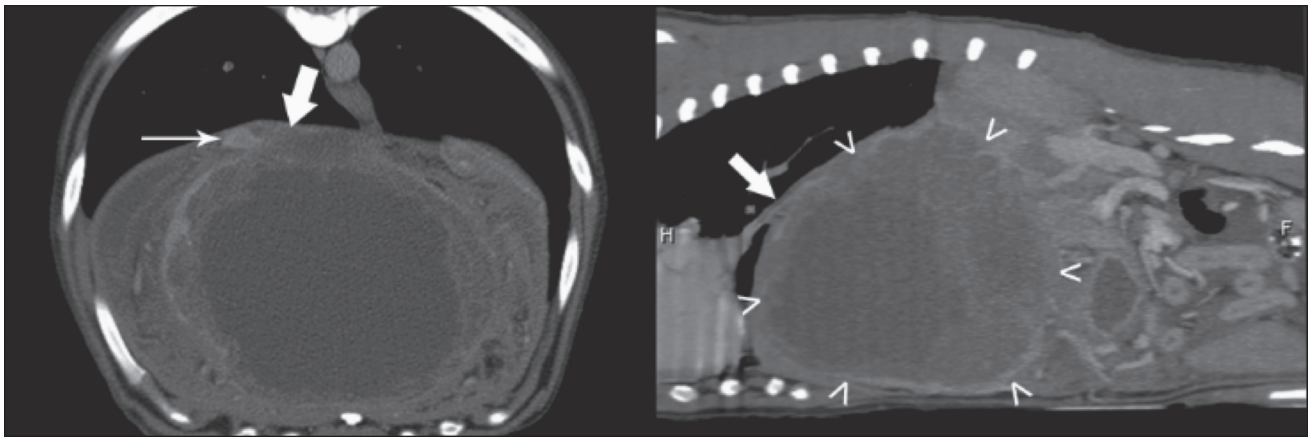

Figure 2. Transverse (left) and right parasagittal reformatting (right), post-contrast CT abdominal scan of the dog at equilibrium. There is a fine rim of enhancement of the fibroinflammatory capsule elements of the largest hepatic *E. multilocularis* lesion (>). Extension of material from the cyst wall (thick arrow) into the caudal vena cava (thin arrow) 6.5 cm cranially to the diaphragm, filling 1/3 of the caval lumen. Ascites is present.

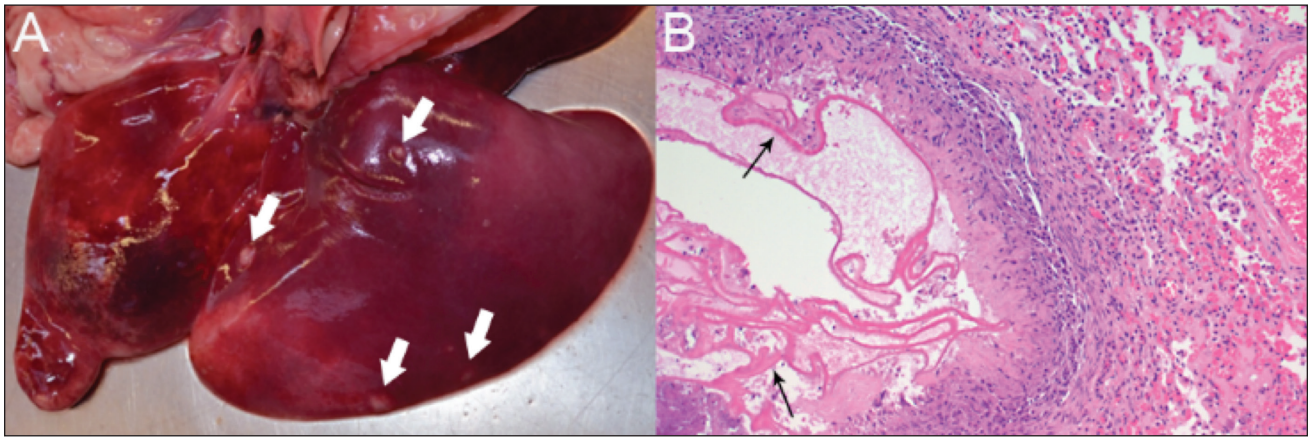

Figure 3. Macroscopic (A) and histologic (B) photographs of lung lesions caused by *E. multilocularis* in the dog. A – randomly distributed, yellow nodules in the lungs (arrows). B – Lung: alveolar hydatid vesicle with outer laminated layer (arrows) surrounded by macrophages, giant cells, lymphocytes, plasma cells and fibrous stroma (H&E stain, magnification 200×).

contours and low attenuation. Intra-lesional calcification and wall calcification may be additional findings. Lateralization of the pulmonary lesions has been observed in humans with *E. granulosus* infections, with approximately 60% occurring in the right lung (5). In the dog in this report, 51 of 73 lesions were right-sided. Primary extrahepatic AE (i.e., in the absence of hepatic lesions) has been documented in 2.3% of patients in one case series (6).

Reports of extrahepatic AE are scarce in veterinary medicine. One report describes AE in the subcutis and thoracic musculature but no internal lesions at autopsy in a 3-year-old Bernese mountain dog (7). A Bavarian group documented 2 dogs with extrahepatic AE lesions (8). The first, similar to the case herein, was a 3.5-year-old Labrador retriever which had histologically confirmed liver and lung AE vesicles. The second dog had a mesenteric AE vesicle the size of a soccer ball in the absence of hepatic or other lesions. Another German group reported on the intraoperative and postmortem appearance of a single pulmonary and multiple hepatic AE lesions in a 2-year-old small Munsterlander in which all masses were histologically diagnosed as granulomatous lesions containing fertile metacestode tissue (9). The pulmonary nodule was a hard white lesion 2 mm in diameter at the caudal border of the right caudal lung lobe. In another case report, a dog presenting with weight loss, acute constipation, and stranguria was found to have AE not only in the liver but also in prostatic and paraprostatic cysts (10). This patient also had pulmonary lesions for which no histologic confirmation of AE could be obtained and which were described as: "several small poorly defined soft tissue opacities in the different lung regions." This differs from findings in the current report, where nodules were sharply delineated and often appeared less attenuating at their core.

Pulmonary AE should not be confused with cystic pulmonary echinococcosis, a term used for the disease caused by *E. granulosus* (2). Canids are the definitive host for the latter parasite, and only rarely develop the large pulmonary cysts seen in intermediate hosts, such as ungulates and occasionally humans (11). To our knowledge, histologically confirmed AE affecting the lungs in dogs has only twice been described in the English, French, and German literature (8,9), and this case report is the first to provide its imaging features.

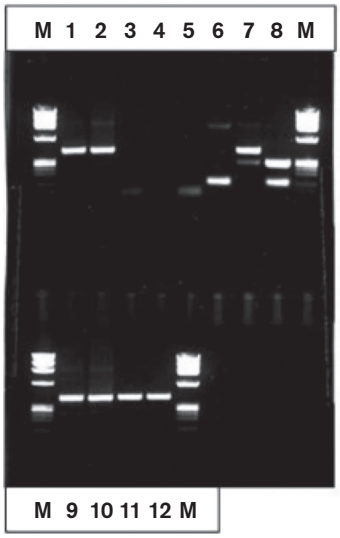

Figure 4. Multiplex PCR shows an amplification product of the same size for hepatic vesicle DNA from the dog in this case report (lanes 1 and 2) as the positive control for *E. multilocularis* (lane 7).

It is said that lung manifestations of AE always occur after involvement of the liver, either through transdiaphragmatic migration, or as we suspect in the case reported herein, through seeding of hepatic lesions invading the vena cava (12).

An interesting feature of *E. multilocularis* is its invasive growth pattern and related mode of metastasis. Lesion growth is independent of the presence of protoscoleces, resulting rather from the proliferation and differentiation of germinal cells found in the germinal layer and cyst fluid (13,14), a process referred to as exogenous proliferation. Release of these germinal cells into the blood stream, lymphatics, or outside the confines of an organ then give rise to new lesions. Extension of cyst wall tissue into the caudal vena cava, although tomographically convincing in our patient, was not specifically assessed during necropsy, and may have been related to the presence of a large number of pulmonary granulomata. In humans, invasion of the inferior vena cava is an unusual presentation of *E. multilocularis,* which may result in metastases to the right atrium and rapidly fatal parasitic pulmonary embolization (12). Rupture of the vena cava into *E. granulosus* cysts and subsequent death have been reported (15,16). Another possible manifestation of hydatid cyst disease, which may be of interest to diagnosticians, is occlusion of hepatic vein flow (Budd-Chiari) or portal vein flow, usually associated with external compression from the cysts rather than invasion. Such events can generally be dealt with by decompression and evacuation of cyst contents (17). Abdominal effusion is present in a minority of cases of AE, and was reported in 4 of 11 dogs in 1 study (4). Analysis of the ascites was not performed in the dog reported herein; however, its presence is explained by the combination of hypoalbuminemia and omental inflammation. There were no CT, surgical, or postmortem clues to caudal vena cava or portal vein obstruction to further explain the effusion.

Of interest to surgeons contemplating cyst resection/radical hepatectomy are the relations between the masses and the portal bifurcation, and in particular evidence of invasion into the main portal vein, hepatic veins or caudal vena cava, and bile ducts. Invasion of bile ducts leads to severe complications in humans, such as cholangitis, biliary cirrhosis, and portal hypertension (3). Nodular proliferations along the large bile ducts diagnosed intraoperatively in our patient were one of the main arguments for euthanasia. These were not only overlooked in CT 1 wk earlier, but could still not be seen retrospectively. Although CT allows adequate anatomic and morphologic characterization of AE lesions, magnetic resonance imaging is recommended in humans for superior depiction of the hepatic vasculature and biliary tree, as well as for exact characterization of parasitic lesion components (3). Magnetic resonance cholangiopancreatography is now the method of choice for assessing the relation between echinococcosis cysts and the biliary tree in surgical planning in humans, but to our knowledge, this method has yet to be described in dogs.

Praziquantel, the only drug approved for the treatment of *E. multilocularis* in the US and UK, is highly effective against the intestinal stage but has no effect on the larval (AE) stage. Concurrent infections of the liver and intestines have been reported in 2 dogs (18). Such cases raise questions about the possibility and mode of autoinfection in this species, and whether the dog in our report at one time harbored intestinal *E. multilocularis*. The prepatent period of *E. multilocularis* (28 to 35 d) warrants, in endemic areas, deworming at 4-week intervals in an effort to control environmental contamination and human exposure (19). Such endemic areas in Canada have historically been limited to the Northern Tundra Zone and to the southern half of the 3 Canadian prairie provinces (11), yet autochtonous cases have lately been recorded outside of the accepted *E. multilocularis* range (20).

Preoperative chemotherapy likely had no effect on the course of the disease in our patient, having been initiated 7 d prior to referral. Long-term chemotherapy with albendazole, based on data from experimental studies with laboratory rodents, appears to have parasitostatic rather than parsitocidal effects (19).

Whether all pulmonary lesions in our patient were AE granulomata could not be determined, as there were too many to assess individually. Small densities up to 3 mm in diameter close to the pleural surface could represent pulmonary osteomata, small fungal granulomas, metastatic disease, and small lesions of unknown significance (21). In endemic regions, *E. multilocularis* should be considered as a differential for nodular lung patterns.

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Book Review
Compte rendu de livre

Small Animal Anesthesia Techniques

Shelby AM, McKune CM. Wiley-Blackwell. Chichester, UK. 2014. 317 pp. ISBN: 9781-1184-2804-7. $54.99 CDN.

This book's stated objective is to provide a reference to anesthesia techniques for dogs, cats, and exotics, and to do so in a way that is straightforward for the veterinary professional. The authors intend to give criteria for creating balanced anesthesia and analgesia, based on their personal preferences and experiences, using research where applicable.

The book is divided into 8 chapters. The first dozen pages describe the anesthetic process by splitting it into 5 steps, starting with the pre-anesthetic assessment and ending with the recovery and post-operative phase. The next chapter provides a brief overview of anesthetic equipment and monitoring. The third chapter offers the reader a comprehensive 60-page table of anesthetic drugs and fluids. The book's middle chapters make recommendations on anesthetic protocols for routine and critical procedures, and for patients with specific diseases. The following chapter on anesthetic complications is formatted according to consequences, causes, and treatment. A later chapter delves into protocols for exotics. The concluding chapter gives the reader step-by-step illustrated techniques of local analgesia. The 9 short appendices cover topics ranging from acute pain scales to epidural calculations.

The book is written clearly and is easy to understand, so it is appropriate for novice and experienced veterinarians and technicians. Color photographs, diagrams, and technique tables with numbered steps make the book user-friendly, and give the reader confidence to successfully carry out procedures. One strength of the book is its third chapter, a detailed outline of the most commonly used drugs and fluids organized in an alphabetized table. The table lists drug qualities such as dosage, duration, characteristics, and complications. Unfortunately, this strong point is weakened by the table missing 30-odd page numbers, which lessens its ease of use. The authors cite interesting new research early in the book, such as using alfaxalone. Disappointingly, later on they fail to incorporate alfaxalone into protocols, without stating a specific reason for the omission.

The book is not a detailed overview of all things anesthesia; rather, it is a guide of specific techniques. If the reader is looking for complete information on topics such as anesthetic equipment, they will need to refer elsewhere. Overall, the authors meet their objective of providing an accessible guide to small animal anesthesia techniques. I would recommend this inexpensive book to veterinarians and technicians alike.

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